SCIENTIFIC ABSTRACT

Cystic fibrosis (CF) is a common, lethal, inherited disease among Caucasian children and young adults. While the pathophysiology of CF includes many organ systems (e.g., gastrointestinal, reproductive, endocrine) the predominant cause of death is respiratory failure. Hyperviscous respiratory secretions and related chronic pulmonary infections lead to scarring and fibrosis of the lungs, deteriorating pulmonary function, and death, with an average CF life expectancy of approximately 29 years. The disease is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. The CFTR functions, at least in part, as an epithelial chloride channel which resides in the apical membranes of exocrine gland epithelial cells. It has been suggested that the fluid and electrolyte content of normal respiratory mucous is dependent upon CFTR chloride channel activity, and that failure to secrete chloride by CF cells results in diminished hydration of mucous, sputum hyperviscosity and the pulmonary sequelae of the disease.

Transfer of normal human CFTR to cells possessing the CF ion transport phenotype (i.e., with defects in Cl^- transport), or into the respiratory epithelium of CF mice leads to re-establishment of CFTR mediated chloride transport. Findings of gene transfer mediated correction of the CF bioelectric defect in these model systems, together with the failure of current therapies to allow CF patients to live beyond young adulthood, indicates the need for new approaches to CF therapy and the possibility of gene transfer-based protocols in the disease. Five gene transfer based protocols using recombinant adenovirus to deliver functional CFTR to limited regions of CF respiratory epithelium *in vivo* have been approved previously for use in humans by the Recombinant DNA Advisory Committee of the N.I.H. Evaluation of the safety and efficacy of adenovirus-based CFTR delivery is currently in progress.

The present protocol is intended to evaluate an alternative, cationic liposome-based mechanism of delivery of normal CFTR to nasal respiratory epithelia of CF patients. The advantages of lipid-based gene transfer are evident, and may include 1) minimal toxicity, 2) less antigenicity than viral DNA delivery vectors, and 3) efficient gene transfer even to non-replicating cells. The nasal airway epithelium is an ideal model for gene transfer of this type, since this epithelium exhibits a CF bioelectric defect and is easily accessable for studies of both safety and efficacy of DNA/vector administration. In addition, the use of this site in CF patients greatly minimizes the risk of serious complications related to gene transfer to the lower airways.